

4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2009-D-0539]

Immunogenicity Testing of Therapeutic Protein Products--Developing and Validating Assays for Anti-Drug Antibody Detection; Guidance for Industry; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of availability.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing the availability of a final guidance for industry entitled "Immunogenicity Testing of Therapeutic Protein Products--Developing and Validating Assays for Anti-Drug Antibody Detection." This guidance provides recommendations to facilitate industry's development and validation of assays for assessment of the immunogenicity of therapeutic protein products during clinical trials. The guidance applies to assays for the detection of anti-drug antibodies (ADAs) and may also apply to some peptides, oligonucleotides, and combination products on a case-by-case basis. The guidance includes recommendations regarding the development and validation of screening assays, confirmatory assays, titration assays, and neutralization assays. This guidance finalizes the revised draft guidance for industry entitled "Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products" issued in April 2016 and includes a revised title.

DATES: The announcement of the guidance is published in the *Federal Register* on **[INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**.

ADDRESSES: You may submit either electronic or written comments on Agency guidances at any time as follows:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2009-D-0539 for "Immunogenicity Testing of Therapeutic Protein Products--Developing and Validating Assays for Anti-Drug Antibody Detection." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about

FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: <https://www.gpo.gov/fdsys/pkg/FR-2015-09-18/pdf/2015-23389.pdf>.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

You may submit comments on any guidance at any time (see 21 CFR 10.115(g)(5)).

Submit written requests for single copies of this guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10001 New Hampshire Ave., Hillandale Building, 4th Floor, Silver Spring, MD 20993-0002; or the Office of Communication, Outreach and Development, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the SUPPLEMENTARY INFORMATION section for electronic access to the guidance document.

FOR FURTHER INFORMATION CONTACT: Ebla Ali-Ibrahim, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6302, Silver Spring, MD 20993, 301-796-3691; or Stephen Ripley, Center for Biologics Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 71, Rm. 7301, Silver Spring, MD 20993-0002, 240-402-7911.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry entitled "Immunogenicity Testing of Therapeutic Protein Products--Developing and Validating Assays for Anti-Drug Antibody Detection." This guidance finalizes the revised draft guidance for industry entitled "Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products" issued in April 2016. Changes made to the guidance took into consideration comments received. In addition to editorial changes primarily for clarification, this guidance includes updated information on titration and confirmatory assays and an additional discussion of immunogenicity risk assessment.

Immune responses to therapeutic protein products have the potential to affect product pharmacokinetics, pharmacodynamics, safety, and efficacy. The clinical effects of patient immune responses are highly variable, ranging from no measurable effect to extremely harmful. Detection and analysis of ADA formation is a helpful tool in understanding potential patient immune responses. Information on immune responses observed during clinical trials, particularly the incidence of ADA induction or any implications of ADA responses affecting pharmacokinetics, pharmacodynamics, safety, and efficacy, is crucial for any therapeutic protein product development program. Accordingly, such information, if applicable, should be included in the prescribing information as a subsection of the ADVERSE REACTIONS section entitled "Immunogenicity."

In general, results from assays for detection of ADA facilitate understanding of the immunogenicity, pharmacokinetics, pharmacodynamics, safety, and efficacy of therapeutic protein products. However, the detection of ADA is dependent on key operating parameters of

the assays (for example, sensitivity, specificity), which vary between assays. Therefore, the development of valid, sensitive, specific, and selective assays to measure ADA responses is a key aspect of therapeutic protein product development.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the current thinking of FDA on "Immunogenicity Testing of Therapeutic Protein Products--Developing and Validating Assays for Anti-Drug Antibody Detection." It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. This guidance is not subject to Executive Order 12866.

II. Paperwork Reduction Act of 1995

This guidance refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The collections of information in 21 CFR part 201 have been approved under OMB control number 0910-0572; the collections of information in 21 CFR part 211 have been approved under OMB control number 0910-0139; the collections of information in 21 CFR part 312 have been approved under OMB control number 0910-0014; the collections of information in 21 CFR part 314 have been approved under OMB control number 0910-0001; the collections of information in 21 CFR part 58 have been approved under OMB control number 0910-0119; and the collections of information in 21 CFR part 601 have been approved under OMB control number 0910-0338.

III. Electronic Access

Persons with access to the internet may obtain the guidance at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, <https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, or <https://www.regulations.gov>.

Dated: January 16, 2019.

Leslie Kux,

Associate Commissioner for Policy.

[FR Doc. 2019-00666 Filed: 1/31/2019 8:45 am; Publication Date: 2/1/2019]